(19) World Intellectual Property Organization

International Bureau





(43) International Publication Date 11 November 2004 (11.11.2004)

PCT

(10) International Publication Number WO 2004/096224 A3

(51) International Patent Classification⁷: A61K 31/496, 31/517, A61P 35/00, A61K 31/404

(21) International Application Number:

PCT/EP2004/004363

(22) International Filing Date: 24 April 2004 (24.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

03009587.1 29 April 2003 (29.04.2003) EP 04000508.4 13 January 2004 (13.01.2004) EP 04001171.0 21 January 2004 (21.01.2004) EP

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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 16 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING CELL PROLIFERATION, MIGRATION OR APOPTOSIS OF MYELOMA CELLS, OR ANGIOGENESIS

(57) Abstract: The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said deseases, coomprising co-administration of effective amounts of specific active compounds and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compounds and/or radiotherapy for the manufacture of corresponding pharmaceutical combination preparations.



International Application No T/EP2004/004363

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61K31/517 A61P35/00 A61K31/404 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category ° US 2003/069299 A1 (WEYER-CZERNILOFSKY 1 - 7ULRIKE ET AL) 10 April 2003 (2003-04-10) page 1, left-hand column, lines 1-26 1-9,WO 03/011837 A (ARRINGTON KENNETH L; χ 13-15, HOFFMAN WILLIAM F (US); FRALEY MARK E 19, (US); MERC) 13 February 2003 (2003-02-13) 21-23, 26,27,30 page 74, lines 13-20; claims WO 03/022815 A (LIANG CONGXIN; TANG PENG 1 - 9CHO (US); BLAKE ROBERT A (US); GUAN HUIPING) 20 March 2003 (2003-03-20) page 3, lines 15-31 page 19, line 26 - page 20, line 4 page 27, line 27 - page 30, line 3 Patent family members are listed in annex. Further documents are listed in the continuation of box C. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not cited to understand the principle or theory underlying the considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another 'Y' document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled other means in the art. document published prior to the international filing date but *&" document member of the same patent family later than the priority date claimed Date of the actual completion of the international search Date of mailing of the international search report 05/11/2004 29 October 2004 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Venturini, F Fax: (+31-70) 340-3016

International Application No /EP2004/004363

		EF2004/004363
C.(Continu Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/070008 A (IMCLONE SYSTEMS INC ;	1-9,
Х	ROCKWELL PATRICIA (US); GOLDSTEIN NEIL I (US)) 12 September 2002 (2002-09-12) cited in the application	13-15, 19, 21-23, 26,27,30
	the whole document	
Р,Х	DE 102 33 500 A (BOEHRINGER INGELHEIM PHARMA) 19 February 2004 (2004-02-19) the whole document	1-15
X	WO 01/32651 A (HENNEQUIN LAURENT FRANCOIS AND; THOMAS ANDREW PETER (GB); ASTRAZENECA) 10 May 2001 (2001-05-10) page 26, line 22 - page 28, line 4 claims	1-10, 13-15
X	US 6 306 874 B1 (ARRINGTON KENNETH L ET AL) 23 October 2001 (2001-10-23)	1-9, 13-15, 19, 21-23, 26,27,30
	column 27, line 10 - column 29, line 40; claims	20,27,30
P,A	WO 03/065995 A (LYONS JOHN ; SUPERGEN INC (US); RUBINFELD JOSEPH (US)) 14 August 2003 (2003-08-14) the whole document	1-30
Α	WO 98/54156 A (MYERS MICHAEL; PERSONS PAUL E (US); SPADA ALFRED P (US); MAGUIRE MART) 3 December 1998 (1998-12-03) the whole document	1-30
Α	DE 199 24 401 A (BOEHRINGER INGELHEIM PHARMA) 30 November 2000 (2000-11-30) the whole document	1-30
Α	DE 100 42 696 A (BOEHRINGER INGELHEIM PHARMA) 14 March 2002 (2002-03-14) the whole document	1-30
Α	WO 97/41844 A (ALCON LAB INC; CLARK ABBOT F (US); DOSHI RUPA (US)) 13 November 1997 (1997-11-13) the whole document	1-30

Information on patent family members

International Application No
/EP2004/004363

Patent document		Publication		Patent family	Publication
cited in search report		date		member(s)	date
US 2003069299	A1	10-04-2003	DE US AU WO EP JP	10054019 A1 2004044222 A1 2004044053 A1 1598002 A 0236564 A1 1341760 A1 2004513113 T	23-05-2002 04-03-2004 04-03-2004 15-05-2002 10-05-2002 10-09-2003 30-04-2004
WO 03011837	Α	13-02-2003	WO	03011837 A1	13-02-2003
WO 03022815	Α	20-03-2003	BR CA EP WO US	0212435 A 2459879 A1 1436259 A1 03022815 A1 2003119819 A1	17-08-2004 20-03-2003 14-07-2004 20-03-2003 26-06-2003
WO 02070008	A	12-09-2002	US BG CZ EE HU NO WO US	2003103973 A1 108214 A 2439933 A1 20032586 A3 200300428 A 1379276 A1 0303378 A2 20033856 A 02070008 A1 2003108545 A1	05-06-2003 30-09-2004 12-09-2002 18-08-2004 15-10-2004 14-01-2004 29-12-2003 03-11-2003 12-09-2002 12-06-2003
DE 10233500	Α	19-02-2004	DE WO US	10233500 A1 2004013099 A1 2004176392 A1	19-02-2004 12-02-2004 09-09-2004
WO 0132651	A	10-05-2001	AU BR CN CEP WU JP NO NZ PK ZA	769222 B2 1288601 A 106659 A 0015203 A 2389767 A1 1387527 T 20021526 A3 200200237 A 1244647 A1 0132651 A1 0203453 A2 3522727 B2 2003513089 T 20022139 A 518028 A 355942 A1 6122002 A3 200202775 A	22-01-2004 14-05-2001 31-03-2003 16-07-2002 10-05-2001 25-12-2002 17-07-2002 16-06-2003 02-10-2002 10-05-2001 28-05-2003 26-04-2004 08-04-2003 03-05-2002 26-03-2004 31-05-2004 09-01-2003 03-12-2003
US 6306874	B1	23-10-2001	AU BG BR CA CN CZ EE	1571001 A 106710 A 0014843 A 2387351 A1 1409708 T 20021390 A3 200200201 A 1226136 A2	30-04-2001 31-03-2003 11-06-2002 26-04-2001 09-04-2003 11-09-2002 16-06-2003 31-07-2002

Information on patent family members

International Application No F/EP2004/004363

		F7/EP2004/004363				
Patent document cited in search report		Publication date		Patent family member(s)	**	Publication date
US 6306874	B1		HR HU JP NO NZ PL SK TR WO US ZA	20020349 0203323 2003512369 20021820 518001 354292 6912002 200201051 0129029 6794393 200202989	A2 T A A A1 A2 A3 A2 A3 A2 B1	29-02-2004 28-02-2003 02-04-2003 23-05-2002 28-05-2004 29-12-2003 05-08-2003 23-09-2002 26-04-2001 21-09-2004 16-04-2003
WO 03065995	Α	14-08-2003	US US CA WO	2003147813 2004127453 2474174 03065995	A1 A1	07-08-2003 01-07-2004 14-08-2003 14-08-2003
WO 9854156	A	03-12-1998	- AUUUUUUGGGRRRAAAANNNAAAPPPUUUUPPPOOOAAALLKKK	747026 7706298 751188 7707998 742739 7803798 103968 104006 9809172 9809501 9809501 9809518 2291750 2291772 1261353 1280572 1140516 2600 4103 0991628 1001948 1	ABABAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	09-05-2002 30-12-1998 08-08-2002 30-12-1998 10-01-2002 30-12-1998 31-07-2000 31-07-2000 01-08-2000 20-06-2000 20-06-2000 20-06-2000 17-01-2001 03-03-2004 27-06-2002 25-12-2003 12-04-2000 24-05-2000 24-05-2000 28-10-2000 28-11-2001 08-05-2002 28-11-2001 08-05-2002 26-11-1999 26-11-1999 26-11-1999 26-11-1999 26-11-1999 26-11-1999 19-11-2002 16-07-2003 31-07-2000 31-07-2000 31-07-2000 31-07-2000 12-06-2000 12-06-2000

Information on patent family members

International Application No
/EP2004/004363

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9854156	A		MO MO	9854156 9854157 9854158	A1	03-12-1998 03-12-1998 03-12-1998
DE 19924401	Α	30-11-2000	DE AU WO	19924401 5215700 0073297	Α	30-11-2000 18-12-2000 07-12-2000
DE 10042696	A	14-03-2002	DE AUG BRACCEWERHUP MOPKUS	2387013 1391557	A A A A A A A A A A A A A A A A A A A	14-03-2002 23-04-2001 31-01-2003 16-07-2002 19-04-2001 15-01-2003 17-07-2002 16-06-2003 19-04-2001 24-07-2002 31-10-2003 28-05-2003 25-03-2003 27-02-2003 11-04-2002 19-04-2004 06-08-2002 13-07-2004
WO 9741844	Α	13-11-1997	AU WO	2438297 9741844		 26-11-1997 13-11-1997